

The influence of barosensory vessel mechanics on the vascular sympathetic baroreflex: insights into aging and blood pressure homeostasis

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American Journal of Physiology - Heart and Circulatory Physiology

DOI:

[10.1152/ajpheart.00265.2020](https://doi.org/10.1152/ajpheart.00265.2020)

Published: 04/08/2020

Peer reviewed version

[Cyswllt i'r cyhoeddiad / Link to publication](#)

Dyfyniad o'r fersiwn a gyhoeddwyd / Citation for published version (APA):

Lord, R., Wakeham, D. J., Pugh, C. J. A., Simpson, L., Talbot, J., Lodge, F. M., Curry, B., Dawkins, T., Shave, R., & Moore, J. (2020). The influence of barosensory vessel mechanics on the vascular sympathetic baroreflex: insights into aging and blood pressure homeostasis. *American Journal of Physiology - Heart and Circulatory Physiology*, 319(2), H370-H376. <https://doi.org/10.1152/ajpheart.00265.2020>

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1 The influence of barosensory vessel mechanics on the vascular sympathetic
2 baroreflex: insights into ageing and blood pressure homeostasis

4 Running title: Barosensory vessel mechanics and the baroreflex

6 Rachel N Lord¹, Denis J Wakeham¹, Christopher JA Pugh¹, Lydia L Simpson³,
7 Jack S Talbot¹, Freya M Lodge², Bryony A Curry¹, Tony G Dawkins¹, Rob E
8 Shave^{1,4}, Jonathan P Moore³

10 1 Cardiff School of Sport and Health Sciences, Cardiff Metropolitan University,
11 United Kingdom;

12 2 Cardiff and Vale University Health Board, University Hospital of Wales,
13 Cardiff, United Kingdom;

14 3 Physical Activity for Health and Well-being (PAWB) Centre, School of Sport,
15 Health and Exercise Sciences, Bangor University, United Kingdom;

16 4 Centre for Heart, Lung, and Vascular Health, University of British Columbia
17 Okanagan, Kelowna, Canada

19 RNL, DJW, RES and JPM contributed to the conception and design of the work

20 RNL, DJW, CJP, LLS, JST, FML, BAC, TGD and JPM contributed to data
21 acquisition, analysis and interpretation of data for the work

22 All authors contributed to drafting the work or revising it critically for important
23 intellectual content, final approval of the version to be published and agree to
24 be accountable for all aspects of the work.

26 Corresponding author:

28 Dr Rachel Lord
29 Cardiff School of Sport and Health Sciences,
30 Cardiff Metropolitan University
31 Cyncoed Road
32 Cardiff

33 United Kingdom
34 CF236XD
35
36 Email: rnlord@cardiffmet.ac.uk
37 Tel: 02920 416373
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ABSTRACT

Changes in the arterial baroreflex arc contribute to elevated sympathetic outflow and altered reflex control of blood pressure with human ageing. Utilizing ultrasound and sympathetic microneurography (muscle sympathetic nerve activity; MSNA) we investigated the relationships between aortic and carotid artery wall tension (indices of baroreceptor activation) and the vascular sympathetic baroreflex operating point (OP; MSNA burst incidence) in healthy, normotensive young ($n = 27$, 23 ± 3 years) and middle-aged men ($n = 22$, 55 ± 4 years). In young men, the OP was positively related to the magnitude and rate of unloading and time spent unloaded in the aortic artery ($r = 0.56$, 0.65 and 0.51 , $P = 0.02$, 0.003 and 0.03), but not related to the magnitude or rate of unloading or time spent unloaded in the carotid artery ($r = -0.32$, -0.07 and 0.06 , $P = 0.25$, 0.81 and 0.85). In contrast, in middle-aged men, the OP was not related to either the magnitude or rate of unloading or time spent unloaded in the aortic ($r = 0.22$, 0.21 and 0.27 , $P = 0.41$, 0.43 and 0.31) or carotid artery ($r = 0.48$, 0.28 and -0.01 , $P = 0.06$, 0.25 and 0.98). In conclusion, in young men, aortic unloading mechanics may play a role in determining the vascular sympathetic baroreflex OP. In contrast, in middle-aged men, barosensory vessel unloading mechanics do not appear to determine the vascular sympathetic baroreflex OP, and therefore do not contribute to age-related arterial baroreflex resetting and increased resting MSNA.

KEYWORDS: muscle sympathetic nerve activity; barosensory vessel unloading mechanics; healthy ageing; sympathetic nervous system; baroreflex

89 **NEW AND NOTEWORTHY**

- 90 • We assessed the influence of barosensory vessel mechanics (magnitude
91 and rate of unloading and time spent unloaded) as a surrogate for
92 baroreceptor unloading.
- 93 • In young men, aortic unloading mechanics are important in regulating the
94 operating point of the vascular sympathetic baroreflex, whereas in
95 middle-aged men, these arterial mechanics do not influence this
96 operating point.
- 97 • The age-related increase in resting muscle sympathetic nerve activity
98 does not appear to be driven by altered baroreceptor input from stiffer
99 barosensory vessels.

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122 **INTRODUCTION**

123 An age-associated increase in arterial blood pressure is evident for apparently
124 healthy humans, and is frequently attributed to structural and functional
125 changes in central arteries (19). Another feature of cardiovascular ageing is the
126 progressive elevation in sympathetic outflow, however this is not necessarily
127 accompanied by increased arterial blood pressure. Over the age of 50 years,
128 ageing results in an upward resetting of the operating point (OP) of the vascular
129 sympathetic baroreflex (20); this occurs with no change in baroreceptor reflex
130 responsiveness, referred to as baroreflex gain (7, 17). In contrast, ageing
131 impairs cardiovagal baroreflex gain (7, 21), indicating a divergent impact of age
132 on the cardiac and vascular components of the arterial baroreceptor reflex. The
133 arterial baroreceptor reflex regulates blood pressure primarily via changes in
134 sympathetic vasomotor activity. Indeed, it is suggested that elevated
135 sympathetic outflow may mitigate age-associated adaptation of the
136 cardiovascular system, and thus preserve homeostatic control of blood pressure
137 (30).

138

139 The vascular sympathetic baroreflex arc consists of mechanoelectrical
140 transduction by arterial baroreceptors, a central neural component, and efferent
141 neurotransmission. Baroreceptors are activated by deformation or strain of the
142 arterial wall where they are located. Therefore, age-related changes within the
143 arterial wall could be an important influence on vascular sympathetic baroreflex
144 resetting with human ageing. Indeed, a study of integrated vascular sympathetic
145 baroreflex control observed that age-related barosensory artery stiffening may
146 alter the mechanical component of baroreflex control of sympathetic outflow.
147 However, overall vascular sympathetic reflex responsiveness appeared to be
148 well maintained (27), which was attributed to more sensitive central neural
149 control. This change may be necessary to offset the age-associated reduction
150 in cardiovagal baroreflex gain; that is, dependence on vascular sympathetic
151 baroreflex control, and outflow, for blood pressure homeostasis increases with
152 advancing age (11). However, increased sympathetic outflow is also associated

153 with an increased risk of developing hypertension and susceptibility to CVD
154 (16). Importantly, mechanism(s) responsible for the age-related rise in
155 sympathetic outflow remain incompletely understood, and it is not clear how
156 these overlap with mechanisms of abnormal sympathoexcitation.

157

158 Previous assessment of the mechanical component of the arterial baroreflex
159 has only quantified the systolic diameter of the common carotid artery in
160 response to the corresponding pressure (10). However, this approach does not
161 give an indication of the magnitude or time course of baroreceptor loading and
162 unloading. Nor does it address mechanical pressure transduction in aortic
163 baroreceptors, which also play an important role in reflex control of sympathetic
164 vasomotor activity. Furthermore, as a burst of MSNA occurs in the diastolic
165 period of the cardiac cycle, a lack of detail about unloading events is, in our
166 view, a notable gap in existing knowledge. Indeed, dynamic events at aortic and
167 carotid baroreceptors may be characterised relatively easily using the
168 magnitude and rate of change in wall tension within these arteries. Therefore,
169 this approach could provide a better index of the baroreceptor stimulus than
170 previous attempts to characterize the mechanical component. That is,
171 acquisition of important information about recoil could be important for
172 developing understanding of reflex control of sympathetic outflow. Notably, it is
173 suggested that the occurrence of a burst of outflow is determined via a central
174 gating mechanism, whereby a burst of sympathetic activity only occurs if there
175 is sufficient time between the removal of afferent inhibition and generation of
176 efferent vasomotor activity within the cardiac cycle (12); this “gate” could be
177 influenced by barosensory vessel wall mechanics. Furthermore, identifying
178 whether stiffer and less compliant arteries (29) and altered vessel wall
179 mechanics contribute to age-related changes in reflex control of MSNA is
180 worthy of consideration.

181

182 With healthy ageing, barosensory vessels are stiffer and less compliant (9, 29)
183 across a wide range of static and dynamic pressures; this may reduce the
184 magnitude and rate of baroreceptor unloading, in barosensory vessels.

185 Hypothetically, this could result in a longer period of reflex inhibition within each
186 cardiac cycle, and subsequently a reduction in MSNA burst probability. In fact,
187 with healthy ageing there is an increase, rather than a decrease, in the
188 proportion of cycles with a burst of activity, that is MSNA burst incidence, or
189 baroreflex OP, increases (18, 23, 28). Consequently, it appears the OP of the
190 vascular sympathetic baroreflex may be regulated independently of
191 barosensory vessel unloading mechanics above a certain age.

192

193 The aim of this study was therefore: 1) to utilise a new method of analysis to
194 effectively quantify dynamic changes in barosensory vessel wall tension as a
195 surrogate for baroreceptor unloading across the cardiac cycle and 2) to
196 establish the impact of the magnitude and rate of unloading and time spent
197 unloaded during the cardiac cycle in the aortic and carotid arteries on the OP of
198 the vascular sympathetic baroreflex in young compared to middle-aged men.
199 We hypothesized that: 1) the magnitude and rate of baroreceptor unloading in
200 the aortic and carotid arteries would be lower, and therefore time spent
201 unloaded, relative to the cardiac cycle, would be shorter, in middle-aged
202 compared to young men and 2) the magnitude and rate of unloading in the
203 aortic and carotid arteries and time spent unloaded, relative to the cardiac cycle,
204 would be related to the OP of the vascular sympathetic baroreflex in young but
205 not middle-aged men.

206

207 **METHODS**

208 **Ethical approval**

209 The study was approved by the Cardiff School of Sport and Health Sciences
210 Research Ethics Committee (Approval code: 16/7/02R) and conformed to the
211 most recent Declaration of Helsinki, except for registration in a database. Prior
212 to testing, participants all provided written informed consent.

213

214 **Participants**

215 Seventy men (age 21-63 years old) were screened to take part in this study.
216 Following exclusion, data were obtained from 27 young men and 22 middle-

217 aged men (see Table 1). All subjects were normotensive and free from
218 diagnosed cardiovascular or metabolic disease and had a BMI of <30.
219 Participants were recruited across a range of fitness status, and all were
220 recreationally active. Participants abstained from caffeine, alcohol and
221 strenuous exercise for twenty-four hours before testing. Participants attended
222 the laboratory on two separate occasions, with visits 1 and 2 separated by a
223 minimum of one week. This study design also facilitated the completion of a
224 previous study (33).

225

226 **Visit 1 - Screening visit and $\dot{V}O_2$ peak testing**

227 Participants attended the laboratory at Cardiff Metropolitan University having
228 eaten >2 hours prior to the testing visit. The first testing session included
229 measures of height (Stadiometer, Holtain Ltd, Crosswell, UK) and body mass
230 (Scales, SECA 770, Vogel & Halke, Hamburg, Germany) to ensure BMI <30
231 $\text{kg}\cdot\text{m}^2$ and resting blood pressure (manual sphygmomanometer, Welch Allyn,
232 UK) to confirm participants were normotensive (<140/90 mmHg supine).
233 Participants also reported both prescription and over the counter medication
234 use and were excluded if regularly taking any form of medication.

235

236 Participants completed an incremental exercise test to exhaustion on a cycle
237 ergometer (Lode Corival, Gronigen, The Netherlands) to assess $\dot{V}O_2$ peak with
238 increments of 20 watts per minute as previously described (33).

239

240 **Visit 2 - Physiological Assessments**

241 On a separate occasion, participants arrived at the laboratory having fasted for
242 six hours. Following 20 minutes of supine rest, participants underwent a period
243 of assessment to quantify sympathetic vasomotor outflow and spontaneous
244 sympathetic baroreflex function. During this time, ultrasound images of the
245 aortic and carotid arteries were obtained for the assessment of the magnitude
246 and rate of unloading, and the time spent unloaded (relative to the cardiac
247 cycle).

248

249 *Hemodynamics and resting sympathetic neural activity*

250 Heart rate (HR) and systolic (SBP) and diastolic blood pressure (DBP) were
251 monitored using a 3-lead ECG and finger photoplethysmography, respectively
252 (FinometerPro, FMS, Groningen, Netherlands). SBP and DBP values were
253 calibrated against manual brachial blood pressure measurements. Mean arterial
254 pressure (MAP) was calculated using the equation $((2 \times \text{DBP}) + \text{SBP})/3$. Multiunit
255 MSNA was obtained from the peroneal nerve by an experienced
256 microneurographer (JPM) in line with current guidelines (28). The acceptability
257 of the MSNA neurogram was based upon established criteria (34) and was
258 amplified, band-pass filtered, rectified and integrated (Nerve Traffic Analyser,
259 Model 663 C, University of Iowa, Iowa City, IA). Once an appropriate site was
260 identified for recording, following 10-minutes of supine rest, baseline MSNA and
261 hemodynamic data were acquired for 10 minutes using a commercial data
262 acquisition system (LabChart 8, LabChart Pro, AD Instruments, UK).
263 Immediately following the 10-minute recording period described above, six
264 minutes of hemodynamic and neural data were recorded during spontaneous
265 breathing to characterize the vascular sympathetic baroreflex regulation of
266 MSNA. Resting MSNA was quantified as burst frequency (bursts per minute
267 $[\text{bursts} \cdot \text{min}^{-1}]$) and the OP of the sympathetic baroreflex was quantified as
268 MSNA burst incidence (bursts per 100 heart beats $[\text{bursts} \cdot 100\text{hb}^{-1}]$). Vascular
269 sympathetic baroreflex gain was assessed using the slope of the stimulus-
270 response relationship between DBP and MSNA burst probability. The MSNA
271 OP was determined from burst incidence (i.e. probability) over the six-minute
272 period.

273

274 *Ultrasound procedures*

275 During 10 minutes of basal MSNA data collection, ultrasound assessment of left
276 ventricular stroke volume and aortic and carotid arteries was undertaken.
277 Echocardiograms were acquired using a commercially available ultrasound
278 system (Vivid E9, GE Medical, Norway) with a 4 MHz array probe. Images were
279 obtained from apical 4 and 2 chamber views of the left ventricle by a single
280 experienced sonographer (RNL) and saved for offline analysis of stroke volume

281 (SV) using Simpson's biplane method, allowing for the calculation of cardiac
282 output (Q_c : HR x SV) and total peripheral resistance (TPR: Q_c /mean arterial
283 pressure). Longitudinal B-mode images (12-MHz linear array transducer, Vivid
284 Q, GE Medical, Norway) of the right common carotid artery 2cm proximal to the
285 carotid bulb were recorded for 1 minute at an insonation angle of 60° for later
286 offline analysis of carotid artery blood flow. Analysis of carotid artery blood flow
287 was performed using semi-automated custom-designed edge-detection and
288 wall-tracking software as outlined previously (35).

289

290 Aortic (4-MHz phased array transducer, Vivid E9, GE Medical, Norway) and
291 carotid artery (12-MHz linear array transducer, Vivid Q, GE Medical, Norway)
292 images were recorded over 15 cardiac cycles by trained sonographers (RNL
293 and CJP). The suprasternal view was used to obtain images of the aortic arch.
294 The right common carotid artery proximal to the carotid bifurcation was used to
295 obtain common carotid artery images. Anatomical M-mode was applied to aortic
296 images between the brachiocephalic and right common carotid artery branches
297 (13), and to carotid artery images 2cm from the carotid bulb (EchoPac BT13,
298 GE Medical, Norway). Systolic diameters of the aorta and carotid arteries were
299 measured as the peak diameter within the systolic period (maximum
300 barosensory vessel stretch) and diastolic diameter was identified as the
301 diameter at the end of barosensory vessel stretch (see Figure 1). Systolic and
302 diastolic wall thickness was measured in both vessel walls at the corresponding
303 M-mode point for systolic and diastolic diameters and an average wall thickness
304 from both walls calculated for 5 cardiac cycles. Systolic and diastolic blood
305 pressure for the corresponding cardiac cycles was identified in the
306 reconstructed arterial pressure signal acquired using Lab Chart. Systolic and
307 diastolic wall tension were then calculated in accordance with previous literature
308 (2, 3) as:

$$\text{Wall tension} = \frac{\text{Pressure} \times \left(\frac{\text{Diameter}}{2}\right)}{\text{Wall thickness}}$$

309

310 The difference between systolic wall tension and diastolic wall tension was used
311 as our measure of the magnitude of baroreceptor unloading. Time calipers were
312 used to determine the time interval between systolic diameter measurement
313 and diastolic diameter measurement to allow calculation of the rate of unloading
314 (time measurement A, Figure 1) as magnitude of unloading/time taken to
315 unload. The time interval between the diastolic diameter measurement and end
316 of the cardiac cycle (time measurement B, Figure 1) was also assessed using
317 time calipers to allow calculation of % of time spent unloaded, relative to the
318 cardiac cycle, as the time taken from the diastolic diameter measurement to the
319 end of the cardiac cycle/cardiac cycle length x 100. See Supplementary Data
320 for cardiac timing methods (<https://doi.org/10.25401/cardiffmet.12145164.v1>).

321

322 (FIGURE 1)

323

324 **Data Analysis**

325 Descriptive statistics were calculated for demographic, anthropometric, and
326 hemodynamic variables. Data are reported as mean \pm SD. Shapiro-Wilk tests of
327 normality were used to assess variable distribution. As all data were normally
328 distributed, independent group T-tests were used to assess between-group
329 differences in participant characteristics, haemodynamics, resting vascular
330 sympathetic baroreflex function and barosensory vessel unloading mechanics.
331 Pearson's correlation coefficients, using $\dot{V}O_2$ peak as a covariate to control for
332 the impact of fitness status, were used to assess the relationship between the
333 magnitude of baroreceptor unloading, the rate of unloading, and the time spent
334 unloaded in the aortic and carotid arteries and the OP and reflex gain of the
335 vascular sympathetic baroreflex. Alpha was set a-priori as $P < 0.05$. All
336 statistical analyses were completed using Statistics Package for Social
337 Sciences for Windows, (Version 23, Chicago, IL).

338 **RESULTS**

339 *Participant characteristics and resting haemodynamics*

340 By design, middle-aged men were significantly older than young men ($P <$
341 0.001), whereas anthropometrics (height, body mass and BMI), and aerobic

342 fitness ($\dot{V}O_2$ peak) were similar between groups ($P > 0.05$, see Table 1).
 343 Resting diastolic blood pressure and HR were similar between young and
 344 middle-aged men. SV and Q_c were all significantly lower in middle-aged men (P
 345 = 0.02 and <0.001 respectively), whereas carotid artery blood flow was not
 346 different between young and middle-aged men. In contrast, TPR and MAP were
 347 significantly elevated with age ($P < 0.003$, see Table 1) and systolic pressure
 348 was elevated, but not significantly, in middle-age. Cardiac timing data are
 349 presented in Supplementary Table 1.

350

351 Table 1 – Participant characteristics and haemodynamics

| | Young men (n = 27) | Middle-aged men (n = 22) |
|---|-----------------------|-----------------------------|
| Age (years) | 23 ± 3 | 55 ± 4 * |
| Height (cm) | 179.1 ± 5.4 | 175.1 ± 6.5 |
| Body mass (kg) | 72.8 ± 12.9 | 72.6 ± 11.4 |
| BMI (kg.m ²) | 23.11 ± 3.82 | 23.67 ± 3.36 |
| SBP (mmHg) | 117 ± 8 | 126 ± 9 |
| DBP (mmHg) | 72 ± 9 | 78 ± 7 |
| MAP (mmHg) | 87 ± 9 | 94 ± 7 * |
| HR (beats.min ⁻¹) | 51 ± 13 | 48 ± 11 |
| SV (ml) | 77 ± 17 | 67 ± 10 * |
| Q_c (L.min ⁻¹) | 3.90 ± 0.59 | 3.11 ± 0.62 * |
| TPR (mmHg.L.min ⁻¹) | 22.54 ± 4.30 | 33.12 ± 5.80 * |
| Carotid artery blood flow (ml.min ⁻¹) | 660 ± 147 | 648 ± 130 |
| $\dot{V}O_2$ peak (ml.kg.min ⁻¹) | 50.4 ± 14.2 | 42.8 ± 11.8 |

352 Data are presented as mean \pm SD. * significantly different between young and
 353 middle-aged men, $P < 0.05$

354

355 *Sympathetic activity and barosensory vessel diameters, wall thickness, wall*
 356 *tension and unloading mechanics*

357 The MSNA OP of the vascular sympathetic baroreflex (i.e. MSNA incidence)
 358 and MSNA burst frequency were both significantly higher in middle-aged men
 359 compared to young men ($P < 0.001$, see Table 2), whereas reflex gain of the
 360 vascular sympathetic baroreflex was similar between groups ($P = 0.51$, see
 361 Table 2).

362

363 Systolic and diastolic wall tension in both the aorta and carotid artery were
 364 similar between young and middle-aged men ($P > 0.05$, see Table 2), therefore,
 365 the magnitude of aortic and carotid artery unloading were not different between
 366 groups ($P = 0.72$ and 0.49 respectively, see Table 2). Despite similar HRs, the
 367 rate of unloading in both the aorta and carotid artery was significantly faster in
 368 young men compared to middle-aged men (both $P < 0.001$, see Table 2).
 369 Consequently, the time spent unloaded relative to the total cardiac cycle length
 370 in both the aorta and carotid artery was significantly greater in young men
 371 compared to middle-aged men ($P = 0.006$ and 0.004 respectively, see Table 2).
 372 Aortic and carotid artery wall thickness and diameter data are presented in
 373 Supplementary Table 2.

374

375 Table 2 – Resting vascular sympathetic baroreflex function and barosensory
 376 vessel unloading mechanics

| | Young men (n = 27) | Middle-aged men (n = 22) |
|---|-----------------------|-----------------------------|
| <i>Vascular sympathetic baroreflex function</i> | | |
| MSNA operating point (burst.100hb ⁻¹) | 32 \pm 20 | 64 \pm 23 * |
| MSNA frequency (burst.min ⁻¹) | 16 \pm 9 | 30 \pm 10 * |

| | | |
|--|----------------|------------------|
| Vascular sympathetic baroreflex gain (%.mmHg ⁻¹) | -6.13 ± 3.02 | -6.03 ± 3.05 |
| <i>Aortic wall tension</i> | | |
| Aortic systolic wall tension (dynes.mm ⁻²) | 854.5 ± 220.3 | 821.4 ± 225.9 |
| Aortic diastolic wall tension (dynes.mm ⁻²) | 358.0 ± 103.5 | 348.1 ± 104.6 |
| <i>Aortic unloading mechanics</i> | | |
| Magnitude of aortic unloading (dynes.mm ⁻²) | 490.0 ± 188.6 | 471.5 ± 143.5 |
| Rate of aortic unloading (dynes.mm ⁻² .ms. ⁻¹) | 1899.7 ± 689.6 | 1146.1 ± 529.9 * |
| Aortic time spent unloaded (%) | 51 ± 9 | 43 ± 10 * |
| <i>Carotid artery wall tension</i> | | |
| Carotid systolic wall tension (dynes.mm ⁻²) | 485.5 ± 153.2 | 470.8 ± 113.4 |
| Carotid diastolic wall tension (dynes.mm ⁻²) | 268.5 ± 98.4 | 232.6 ± 58.6 |
| <i>Carotid artery unloading mechanics</i> | | |
| Magnitude of carotid unloading (dynes.mm ⁻²) | 222.3 ± 79.4 | 238.2 ± 69.5 |
| Rate of carotid unloading (dynes.mm ⁻² .ms. ⁻¹) | 844.0 ± 380.4 | 421.8 ± 191.6 * |
| Carotid time spent unloaded (%) | 50 ± 8 | 41 ± 11 * |

377 Data are presented as mean ± SD. * significantly different between young and
378 middle-aged men, $P < 0.05$

379

380

381 *Relationships between operating point of vascular sympathetic baroreflex and*
382 *barosensory vessel unloading mechanics*

383 In young men, the MSNA OP of the vascular sympathetic baroreflex was
384 positively related to the magnitude of aortic unloading, the rate of aortic
385 unloading and time spent unloaded in the aorta ($P < 0.03$, see Figure 2), but

was not related to the magnitude of carotid unloading, the rate of carotid unloading or time spent unloaded in the carotid artery ($P > 0.05$, see Table 3). In contrast, in middle-aged men, the MSNA OP of the vascular sympathetic baroreflex was not related to the magnitude of either aortic or carotid artery unloading, the rate of unloading or the time spent unloaded in either aorta or carotid artery ($P > 0.05$, see Figure 2 and Table 3). In young men, the magnitude of aortic but not carotid artery unloading was related to vascular sympathetic baroreflex gain ($P = 0.03$, see Figure 3), whereas in middle-aged men the magnitude of neither aortic nor carotid artery unloading was related to vascular sympathetic baroreflex gain. In both young and middle-aged men, neither the rate of unloading or time spent unloaded was related to vascular sympathetic baroreflex gain.

(FIGURE 2)

(FIGURE 3)

Table 3 - Relationships between the magnitude of carotid unloading, rate of unloading and time spent unloaded and the MSNA OP of the vascular sympathetic baroreflex

| | Young men (n = 27) | | Middle-aged men (n = 22) | |
|---|-----------------------|----------|-----------------------------|----------|
| | <i>r</i> | <i>P</i> | <i>r</i> | <i>P</i> |
| | value | value | value | value |
| <i>Relationship with MSNA operating point</i> | | | | |
| Magnitude of aortic unloading (dynes.mm ⁻²) | 0.56 | 0.02* | 0.22 | 0.41 |
| Rate of aortic unloading (dynes.mm ⁻² .ms. ⁻¹) | 0.65 | 0.003* | 0.21 | 0.43 |
| Aortic time unloaded (%) | 0.51 | 0.03* | 0.27 | 0.31 |
| <i>Relationship with MSNA operating point</i> | | | | |
| Magnitude of carotid unloading | -0.32 | 0.25 | 0.06 | 0.48 |

| | | | | | |
|--|--|-------|------|-------|------|
| | (dynes.mm ⁻²) | | | | |
| | Rate of carotid unloading | -0.07 | 0.81 | 0.28 | 0.25 |
| | (dynes.mm ⁻² .ms. ⁻¹) | | | | |
| | Carotid time unloaded (%) | 0.06 | 0.85 | -0.01 | 0.98 |

* significant relationship, $P < 0.05$

DISCUSSION

Our primary aim was to use a new methodological approach to investigate relationships between indices of barosensory vessel unloading mechanics and indices of vascular sympathetic baroreflex function. Therefore, we determined the following: the magnitude of aortic and carotid artery unloading, the rate of unloading, and the time spent unloaded (%); and, vascular sympathetic baroreflex MSNA OP and gain. The key findings are threefold: 1) in young men, aortic unloading mechanics, but not carotid artery unloading mechanics, are related to the OP of the vascular sympathetic baroreflex, implying that the aortic unloading mechanics may be important in regulating this OP, whereas carotid artery unloading mechanics are not, 2) in middle-aged men, neither aortic nor carotid artery unloading mechanics are related to the OP of the vascular sympathetic baroreflex, suggesting that barosensory vessel unloading mechanics likely do not have a role in determining this OP with advancing age, and 3) in young men, but not middle-aged men, aortic unloading is related to the reflex gain of the vascular sympathetic baroreflex, indicating that reflex responsiveness is not dependent upon unloading mechanics in healthy older men. These key findings provide new insight into reflex control of sympathetic outflow and the mechanisms underlying age-related vascular sympathetic baroreflex resetting.

Impact of barosensory vessel unloading mechanics on baroreflex function in young men

The key novel aspect of the study was measurement of the magnitude and rate of change in wall tension within the arterial walls of barosensory vessels during

434 the recoil phase of mechanical deformation. For the younger men studied here,
435 a striking finding is that aortic unloading, the rate of unloading, and the time
436 spent unloaded in the aorta all correlated positively with the MSNA OP. The
437 potential role that aortic vessel unloading mechanics play in determining the OP
438 of the vascular sympathetic baroreflex in young men may be explained by the
439 interaction between these mechanics and the potential for a burst to occur via
440 the proposed “gate” system (12). Presumably, a shorter proportion of the
441 cardiac cycle with baroreceptor afferent input to the nucleus tractus solitarius
442 (NTS), would increase the likelihood of a burst, dependent upon a sufficient
443 period between the removal of inhibition and initiation of a burst of efferent
444 activity within the cardiac cycle (12). Over time, in the resting state, the rate of
445 unloading and time spent unloaded may therefore represent an important
446 control input to the brainstem in determining the OP of the sympathetic
447 baroreflex in young men. Indeed, animal data supports the notion that
448 baroreceptors have a long-term control input on resting SNA (32).

449

450 Furthermore, only the magnitude of aortic unloading was related to reflex gain
451 of the vascular sympathetic baroreflex in the young men studied here. This is
452 intriguing given that arterial baroreceptors are located at both sites. Previous
453 studies have suggested that the aortic baroreflex is more important than the
454 carotid baroreflex in blood pressure regulation in young men (26) and that aortic
455 baroreceptors have a higher pressure mechanosensitivity than carotid
456 baroreceptors (15). In addition, the aortic baroreflex in isolation can produce a
457 sustained inhibition of MSNA, whereas the carotid baroreflex cannot achieve
458 this (26). Aortic distensibility has also been shown to be more important than
459 carotid distensibility with respect to cardiovagal baroreflex gain (13); however,
460 until now, no studies have determined the relative contribution of the aortic and
461 carotid artery to vascular sympathetic baroreflex gain.

462

463 *Impact of barosensory vessel unloading mechanics on baroreflex function in*
464 *middle-age*

465 In this study, we observe proportionately less time *per* cardiac cycle with the
466 baroreceptors unloaded in middle-aged men compared with younger
467 individuals. Despite this, older men operate with predictably higher MSNA burst
468 probability. There is, however, no relationship between unloading mechanics in
469 barosensory vessels and sympathetic baroreflex OP or reflex gain. It seems
470 reasonable, therefore, to speculate that age-related resetting of the vascular
471 sympathetic baroreflex is not determined by altered barosensory vessel
472 unloading mechanics. We cannot, however, discount changes at the
473 baroreceptors themselves, and/or changes in central mechanisms that generate
474 and modulate MSNA (see below).

475

476 Neither aortic nor carotid artery unloading mechanics were related to reflex gain
477 of the vascular sympathetic baroreflex in middle-aged men, implying that
478 unloading does not have an important role in determining baroreflex
479 responsiveness in this age group. However, our data contrasts with a previous
480 study reporting a significant negative correlation between barosensory vessel
481 distensibility and reflex gain of the vascular sympathetic baroreflex (24); this
482 difference could be explained by an older sample population, of approximately
483 15 years, for that study compared to the middle-aged cohort examined in the
484 present study; or, the different methodology used to quantify the mechanical
485 component of reflex gain.

486

487 *Potential modulators of the operating point of the vascular sympathetic* 488 *baroreflex*

489 A potential mechanism to explain why unloading mechanics of barosensory
490 vessels do not determine the MSNA OP of the vascular sympathetic baroreflex
491 in middle-aged men could be related to adaptation of the baroreceptor with age.
492 Animal studies show that baroreceptor activity declines following a period of
493 sustained pressure elevation with increased vessel stiffness (6). Moreover,
494 increased vessel stiffness with age is related to reduced stretch sensitivity (1),
495 and therefore a higher threshold to initiate baroreceptor afferent activity is
496 evident (5). Either the combination of these adaptations, or one in isolation,

497 would cause reduced baroreceptor afferent firing at a given pulsatile pressure
498 (31) and therefore elevate the OP of the vascular sympathetic baroreflex,
499 independent of barosensory vessel mechanics; however this cannot be
500 assessed easily *in vivo* in humans.

501 The possibility that central neural remodeling may also alter sympathetic outflow
502 at rest is conceivable (4). Cerebral noradrenaline turnover increases with age
503 (8) which may be a contributor to increased central sympathetic outflow. Indeed,
504 animal studies have suggested brain structures that influence baroreceptor
505 control of sympathetic bursts (22) and brain imaging studies in humans also
506 support these structures as regions of baroreflex control (14). In addition,
507 Osborn and colleagues (2005) propose that there is a baroreceptor-
508 independent central nervous system set point for sympathetic outflow to the
509 kidney (25). Taken together, these data suggest that neural plasticity may
510 result in a central resetting of sympathetic outflow, distinct to barosensory
511 vessel mechanical input.

512

513 *Limitations*

514 The association between spontaneous fluctuations in DBP and occurrence of
515 bursts of MSNA were used to calculate vascular sympathetic baroreflex gain,
516 therefore we did not take burst amplitude into account in our analysis.
517 Baroreceptor signals modulate burst occurrence via a gating system (12),
518 whereas little is known about the mechanisms that control burst amplitude. In
519 addition, we did not assess vascular sympathetic reflex gain to rising and falling
520 pressure independently and therefore do not have a measure of baroreflex
521 hysteresis in our data (27). Given the *a priori* aim of this study, we do not
522 present data relating these vessel unloading mechanics to MSNA burst
523 frequency. However, post hoc analysis of our data revealed the same significant
524 relationships as we report with the MSNA OP in young but not middle-aged
525 men.

526

527 We have not reported the relationships between barosensory vessel unloading
528 mechanics and the OP or gain of the cardiovagal baroreflex, as it is not known
529 whether the cardiovagal baroreflex also operates via a similar gating system.
530 That said, our data demonstrates the same significant relationships as we
531 report with the MSNA OP in young but not middle-aged men. In this exploratory
532 investigation, we only examined men and therefore further studies with female
533 participants across the age range are required to establish potential sex
534 differences.

535

536 The data we obtained for carotid unloading was acquired from the common
537 carotid artery which does not harbour baroreceptors, these are located in the
538 carotid sinus. However, previous studies imaging both aortic and carotid artery
539 sinus have only reported a significant contribution from the aorta, not carotid
540 sinus, to cardiovagal baroreflex gain (13) and previous studies assessing the
541 mechanical component of both the cardiovagal (10) and sympathetic baroreflex
542 (27) have imaged the common carotid artery, not the carotid sinus.

543

544 *Future research directions*

545 This study is the first to apply this new methodology and suggest a control input
546 for unloading mechanics on the MSNA OP. Further investigation designed to
547 influence unloading mechanics using manipulations of volume/pressure in
548 barosensory vessels, and beat-by-beat analysis of this response, are required
549 to establish the importance of unloading mechanics in determining the OP of
550 the vascular sympathetic baroreflex. In addition, the impact of unloading
551 mechanics on burst amplitude, onset and latency should be explored.

552

553 **PERSPECTIVES**

554 In our view, the increase in MSNA with healthy ageing may indicate an
555 increased dependence on the vascular sympathetic baroreflex to maintain
556 blood pressure. Notably, we find that the MSNA OP of the vascular
557 sympathetic baroreflex of healthy middle-aged men is not related to aortic or
558 carotid artery unloading mechanics. In contrast, indices of aortic unloading

559 mechanics are associated with the MSNA OP, and reflex gain, for younger men.
560 Thus, we infer that age-related elevation of MSNA OP and basal sympathetic
561 outflow is not driven by vascular ageing and stiffening of barosensitive vessel
562 walls. Although not tested here, central mechanisms that subserve baroreflex
563 resetting likely underpin elevated basal vasomotor outflow with human ageing.
564 Nevertheless, abnormally elevated sympathetic nervous system activity is a
565 feature of hypertension and other diseases of the circulation. Therefore, further
566 exploration of mechanism(s) responsible for increased central sympathetic
567 outflow, and delineating physiological from pathological processes, is
568 fundamental to our understanding of the progression of hypertension and other
569 CVD.

570

571

572 **CONCLUSIONS**

573 This study demonstrates that in young, healthy, normotensive men, aortic
574 unloading mechanics contribute to the resting OP of the vascular sympathetic
575 baroreflex, whereas carotid artery unloading mechanics do not influence this
576 OP. With advancing age, neither aortic nor carotid artery unloading mechanics
577 have a role in determining the resting OP of the vascular sympathetic
578 baroreflex. Taken together, these data suggest that although advancing age
579 alters barosensory vessel unloading mechanics, these mechanics do not control
580 the OP of the vascular sympathetic baroreflex in middle-aged men, and are
581 therefore not driving the well documented age-related increase in resting
582 MSNA.

583
584 **Acknowledgments**

585 We would like to thank our participants for volunteering the time to complete this
586 study.

587
588 **Source(s) of Funding**

589 None

590
591 **Conflict(s) of Interest/Disclosure(s)**

592 None

593
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705

706

707 **FIGURE LEGENDS**

708 Figure 1 – Example of aortic wall thickness measurement (blue line) and aortic
709 diameter measurement (red line) in systole and diastole for one cardiac cycle.
710 “A” indicates the time caliper measurement between systolic and diastolic
711 diameters (time taken to unload) and “B” indicates the time caliper
712 measurement between diastolic diameter measurement and end of the cardiac
713 cycle (time spent unloaded).

714

715 Figure 2 – Relationships between the magnitude of aortic unloading, rate of
716 unloading and time spent unloaded and the MSNA OP of the vascular
717 sympathetic baroreflex in young (filled circles) and middle-aged men (open
718 diamonds)

719

720 Figure 3 - Relationships between aortic unloading and vascular sympathetic
721 baroreflex gain in young (filled circles) and middle-aged men (open diamonds)

722

723

Table 1 – Participant characteristics and haemodynamics

| | Young men (n = 27) | Middle-aged men (n = 22) |
|---|-----------------------|-----------------------------|
| Age (years) | 23 ± 3 | 55 ± 4 * |
| Height (cm) | 179.1 ± 5.4 | 175.1 ± 6.5 |
| Body mass (kg) | 72.8 ± 12.9 | 72.6 ± 11.4 |
| BMI (kg.m ²) | 23.11 ± 3.82 | 23.67 ± 3.36 |
| SBP (mmHg) | 117 ± 8 | 126 ± 9 |
| DBP (mmHg) | 72 ± 9 | 78 ± 7 |
| MAP (mmHg) | 87 ± 9 | 94 ± 7 * |
| HR (beats.min ⁻¹) | 51 ± 13 | 48 ± 11 |
| SV (ml) | 77 ± 17 | 67 ± 10 * |
| Q _c (L.min ⁻¹) | 3.90 ± 0.59 | 3.11 ± 0.62 * |
| TPR (mmHg.L.min ⁻¹) | 22.54 ± 4.30 | 33.12 ± 5.80 * |
| Carotid artery blood flow (ml.min ⁻¹) | 660 ± 147 | 648 ± 130 |
| $\dot{V}O_2$ peak (ml.kg.min ⁻¹) | 50.4 ± 14.2 | 42.8 ± 11.8 |

Data are presented as mean ± SD. * significantly different between young and middle-aged men, $P < 0.05$

Table 2 – Resting vascular sympathetic baroreflex function and barosensory vessel unloading mechanics

| | Young men (n = 27) | Middle-aged men (n = 22) |
|--|-----------------------|-----------------------------|
| <i>Vascular sympathetic baroreflex function</i> | | |
| MSNA operating point (burst.100hb ⁻¹) | 32 ± 20 | 64 ± 23 * |
| MSNA frequency (burst.min ⁻¹) | 16 ± 9 | 30 ± 10 * |
| Vascular sympathetic baroreflex gain (%.mmHg ⁻¹) | -6.13 ± 3.02 | -6.03 ± 3.05 |
| <i>Aortic wall tension</i> | | |
| Aortic systolic wall tension (dynes.mm ⁻²) | 854.5 ± 220.3 | 821.4 ± 225.9 |
| Aortic diastolic wall tension (dynes.mm ⁻²) | 358.0 ± 103.5 | 348.1 ± 104.6 |
| <i>Aortic unloading mechanics</i> | | |
| Magnitude of aortic unloading (dynes.mm ⁻²) | 490.0 ± 188.6 | 471.5 ± 143.5 |
| Rate of aortic unloading (dynes.mm ⁻² .ms. ⁻¹) | 1899.7 ± 689.6 | 1146.1 ± 529.9 * |
| Aortic time spent unloaded (%) | 51 ± 9 | 43 ± 10 * |
| <i>Carotid artery wall tension</i> | | |
| Carotid systolic wall tension (dynes.mm ⁻²) | 485.5 ± 153.2 | 470.8 ± 113.4 |
| Carotid diastolic wall tension (dynes.mm ⁻²) | 268.5 ± 98.4 | 232.6 ± 58.6 |
| <i>Carotid artery unloading mechanics</i> | | |
| Magnitude of carotid unloading (dynes.mm ⁻²) | 222.3 ± 79.4 | 238.2 ± 69.5 |
| Rate of carotid unloading (dynes.mm ⁻² .ms. ⁻¹) | 844.0 ± 380.4 | 421.8 ± 191.6 * |
| Carotid time spent unloaded (%) | 50 ± 8 | 41 ± 11 * |

Data are presented as mean ± SD. * significantly different between young and middle-aged men, $P < 0.05$

Table 3 - Relationships between the magnitude of carotid unloading, rate of unloading and time spent unloaded and the MSNA OP of the vascular sympathetic baroreflex

| | Young men (n = 27) | | Middle-aged men (n = 22) | |
|---|-----------------------|----------|-----------------------------|----------|
| | <i>r</i> | <i>P</i> | <i>r</i> | <i>P</i> |
| | value | value | value | value |
| <i>Relationship with MSNA operating point</i> | | | | |
| Magnitude of aortic unloading (dynes.mm ⁻²) | 0.56 | 0.02* | 0.22 | 0.41 |
| Rate of aortic unloading (dynes.mm ⁻² .ms. ⁻¹) | 0.65 | 0.003* | 0.21 | 0.43 |
| Aortic time unloaded (%) | 0.51 | 0.03* | 0.27 | 0.31 |
| <i>Relationship with MSNA operating point</i> | | | | |
| Magnitude of carotid unloading (dynes.mm ⁻²) | -0.32 | 0.25 | 0.06 | 0.48 |
| Rate of carotid unloading (dynes.mm ⁻² .ms. ⁻¹) | -0.07 | 0.81 | 0.28 | 0.25 |
| Carotid time unloaded (%) | 0.06 | 0.85 | -0.01 | 0.98 |

* significant relationship, $P < 0.05$





